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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/798,884	03/12/2004	Viswanathan Srinivasan	P24615	4898

7055 7590 06/25/2009

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EXAMINER	
SASAN, ARADHANA	
ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
06/25/2009	ELECTRONIC

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/798,884
Filing Date: March 12, 2004
Appellant(s): SRINIVASAN ET AL.

Stephen M. Roylance
For Appellant

EXAMINER'S ANSWER

Please note that the Examiner's Answer of 01/23/2009 is being vacated.

This is in response to the appeal brief filed 10/20/08 appealing from the Office action mailed 10/19/07.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

A Notice of Appeal was filed on February 25, 2008 in co- pending and commonly assigned Application No. 10/736,902, which application contains claims over which some of the present claims have provisionally been rejected on the ground of nonstatutory obviousness-type double patenting (see page 14, section 19 of the Final Office Action mailed October 19, 2007).

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows: New grounds of rejection for claim 48 follow (Please see section (9)).

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

The prior art relied on is as follows:

Fanara et al. (US 6,699,502 B1)

Jaeger (US 3,914,425)

Findlay et al. (US 4,650,807)

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-3, 18-21, 78, 80, 92-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fanara et al. (US 6,699,502).

The claimed invention is a pharmaceutical dosage form that contains a morphine derivative with antitussive activity in combination with at least one additional active ingredient. The dosage form releases the morphine derivative and the additional active ingredient at rates that provide pharmaceutically suitable plasma concentrations over similar periods of time. The dosage form comprises tablets, bi-layered tablets, and multi-layered tablets.

Fanara teaches a pharmaceutical composition (including a multi-layered pharmaceutical composition) for oral administration that allows the release of at least one active substance and includes a matrix (Abstract). Fanara teaches, "the release of active substances during oral administration can be controlled by means of matrix-type pharmaceutical compositions" (Col. 1, lines 14-16). The compositions "can be administered in a few daily doses, ideally in a single daily dose" (Col. 1, lines 9-13). Fanara further teaches, "it is increasingly advantageous to be able to simultaneously administer by oral route an active substance released immediately after administration, and the same or a second active substance released gradually and regularly after administration ... this makes it possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles" (Col. 2, lines 36-50). This reference also teaches that "controlled-release pharmaceutical compositions can be used in combination with an immediate-release pharmaceutical composition for the same or for another active substance, in a single unit intended to be administered orally" (Col. 3, lines 32-37). Antihistamines, antitussives, such as codeine, morphine, and their pharmaceutically acceptable salts, along with pseudoephedrine, and phenylepherine may be included in the composition (Col. 4, lines 54-67). The pharmaceutical composition can be in the form of tablets (Col. 5, lines 18-20). The tablets can be bilayered (Col. 5, lines 48-58) or multilayered (Col. 6, lines 20-26). Example 7 of this reference discloses a double-layer tablet (with the two layers stuck to each other) containing 15mg doses

of hydrocodone bitartrate (10mg of the hydrocodone is in a controlled release layer and 5mg of the hydrocodone is in an immediate release layer (Col. 12, line 25-64).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the pharmaceutical composition having combined therapeutic effects of more than one active substance, as suggested by Fanara, and produce the instant invention.

The pharmaceutical dosage form comprising a first drug (morphine derivative having antitussive activity) and a second drug where the dosage form provides a plasma concentration within a therapeutic range of the second drug over a period which is coextensive with at least about 70% of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug would have been obvious to one of ordinary skill in the art over Fanara. As mentioned above, Fanara teaches simultaneously administering more than one active substance and combining the therapeutic effects of active substances with different pharmacokinetic profiles (Col. 2, lines 36-50) and includes antitussives, antihistamines, codeine, and morphine as possible active substances in the composition. In order to have the combined therapeutic effects of active substances, it would have been obvious to one with ordinary skill in the art that the period of therapeutic effectiveness of the first active substance would be coextensive with the period of therapeutic effectiveness of the second active substance, especially if the two active substances are related to similar (antitussive) therapeutic activities.

Regarding instant claims 18-21, the tablet (bilayered) and comprising a matrix with the first drug and particles with the second drug would have been obvious to a person with ordinary skill in the art over the Fanara teaching of bilayered tablets and matrix.

One of ordinary skill in the art would have been motivated to do this because the pharmaceutical composition as taught by Fanara allows the release of the "active substances such that a satisfactory therapeutic effect is observed over fairly long periods, for example in only one or even two daily doses" (Col. 3, lines 22-27).

3. Claims 4-7, (12-14), 15-17, 23-29, 30-36, 38-44, 47, 49-52, 72-77, 81-87 and new claims 99-111, 114-116 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fanara et al. (US 6,699,502) as applied to claims 1-3, 18-21, 78, 80, 92-96, above, in view of Jaeger (US 3,914,425).

The teaching of Fanara is stated above.

Fanara does not expressly teach codeine phosphate as the active substance.

Jaeger teaches an antitussive codeine composition. Example 2 of this reference illustrates a three-layer "pill" or tablet containing codeine phosphate (Col. 2, lines 43-47). "An intermediate layer containing 6mg each of the two active ingredients was protected by a thin coating ... and the outer layer contained 18mg codeine phosphate". Jaeger also teaches "preparations containing codeine may additionally contain antihistamines such as triprolidine hydrochloride, decongestants such as

pseudoephedrine hydrochloride, and expectorants such as glyceryl guaiacolate" (Col. 3, lines 3-7).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the pharmaceutical composition having combined therapeutic effects of more than one active substance, as suggested by Fanara, in view of the codeine phosphate and second active substances (antihistamines, decongestants, and expectorants) as suggested by Jaeger and produce the instant invention.

Regarding instant claims 51-52, one with ordinary skill in the art would use the teachings of Fanara and Jaeger to produce tablets with multiple layers, where the multiple layers were adjacent to each other, or one layer surrounding the other.

Regarding instant claims 12-14, 47, and 73 one with ordinary skill in the art would use the teachings of Fanara and Jaeger to make a pharmaceutical composition by using drug combinations (antitussives, antihistamines, decongestants, expectorants) with drugs having different plasma half-lives in order to optimize the release of drugs over time. Drugs that are part of the immediate release would have a different plasma half-life than drugs that are part of the controlled release in order to maintain drug release for optimal therapeutic effect.

Regarding instant claims 15-17, 28-29, and 72-74, one with ordinary skill in the art would use the teachings of Fanara and Jaeger to make pharmaceutical compositions using drugs with different pharmacokinetic profiles (Fanara, Col. 2, lines 46-50). The claim limitations of periods of plasma concentration within the

therapeutic range of the second drug being coextensive with at least about 80%, 90% or 95% of periods of plasma concentration within the therapeutic range of the first drug would have been obvious over the different pharmacokinetic profiles taught by Fanara in view of the antitussive codeine composition taught by Jaeger.

Regarding instant claims 97-98, a person with ordinary skill in the art would use the teachings of Fanara and Jaeger to make a pharmaceutical dosage form with a morphine derivative as the first drug and the second drug. Furthermore, Fanara also teaches, "as regards the dose of active substance used, it depends on the effective dose and may therefore vary within very wide limits depending on the said active substance" (Col. 5, lines 1-3). A person with ordinary skill in the art would formulate the composition in order to optimize the plasma concentration of the morphine derivative so that release of the morphine derivative from the two layers does not exceed the safe limit (maximum plasma concentration of the therapeutic range) of the morphine derivative.

One of ordinary skill in the art would have been motivated to do this because the pharmaceutical composition as taught by Fanara allows the release of the "active substances such that a satisfactory therapeutic effect is observed over fairly long periods, for example in only one or even two daily doses" (Col. 3, lines 22-27). The second drugs taught by Jaeger would have been obvious to one of ordinary in the art as supplementing the antitussive first drugs for ameliorating cough symptoms.

4. Claims 8-11, 37, 45-46, and new claims 112-113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fanara et al. (US 6,699,502) as applied to claims 4-

7, 15-17, 23-29, 30-36, 38-44, 47, 49-52, 72-77, 81-87, and 97-98, above, in view of Jaeger (US 3,914,425) and further in view of Findlay et al. (US 4,650,807).

The teachings of Fanara and Jaeger are stated above.

Fanara and Jaeger do not expressly teach chlorpheniramine, promethazine, and guaifenesin.

Findlay teaches antihistaminic compositions. These compositions include tablets (Col. 5, lines 33-35). Antihistamines such as pheniramines, and promethazine are disclosed (Col. 1, lines 26-28). It is also taught that, "the active compound may be formulated with a sympathomimetic agent such as decongestants pseudoephedrine or phenylpropanolamine, an antitussive such as codeine ... or an expectorant such as guaifenesin" (Col. 5, lines 9-15).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the pharmaceutical composition with combined therapeutic effects of more than one active substance, as suggested by Fanara, in view of the codeine phosphate and second active substances (antihistamines, decongestants, and expectorants) as suggested by Jaeger and further in view of the specific antihistamines and expectorant as suggested by Findlay and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because the specific active substances taught by Findlay supplement the antitussive first drugs for ameliorating cough symptoms.

NEW GROUND(S) OF REJECTION

Claim Rejections - 35 USC § 103

5. Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fanara et al. (US 6,699,502), in view of Jaeger (US 3,914,425).

Claim 48 is drawn to the multi-layered tablet of claim 47, wherein the tablet provides a plasma concentration within a therapeutic range of the at least one drug in the second layer over a period which is coextensive with at least about 80% of a period over which the tablet provides a plasma concentration within a therapeutic range of the at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

The teaching of Fanara is stated above.

Fanara does not expressly teach codeine phosphate as the active substance.

Jaeger teaches an antitussive codeine composition. Example 2 of this reference illustrates a three-layer "pill" or tablet containing codeine phosphate (Col. 2, lines 43-47). "An intermediate layer containing 6mg each of the two active ingredients was protected by a thin coating ... and the outer layer contained 18mg codeine phosphate". Jaeger also teaches "preparations containing codeine may additionally contain antihistamines such as triprolidine hydrochloride, decongestants such as pseudoephedrine hydrochloride, and expectorants such as glyceryl guaiacolate" (Col. 3, lines 3-7).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the pharmaceutical composition having combined therapeutic effects of more than one active substance, as suggested by Fanara, in view of the codeine phosphate and second active substances (antihistamines, decongestants, and expectorants) as suggested by Jaeger and produce the instant invention.

Regarding instant claim 48, one with ordinary skill in the art would use the teachings of Fanara and Jaeger to make a pharmaceutical composition by using drug combinations (antitussives, antihistamines, decongestants, expectorants) with drugs having different plasma half-lives in order to optimize the release of drugs over time. Drugs that are part of the immediate release would have a different plasma half-life than drugs that are part of the controlled release in order to maintain drug release for optimal therapeutic effect.

(10) Response to Argument

10-a. Appellants argue that Fanara fails to render obvious independent claim 1.

Appellants argue that the Examiner's conclusions with respect to Fanara are based on hindsight.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was

within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

> Appellants state that FANARA is concerned primarily with pharmaceutical compositions for the controlled release of active substances (see, e.g., title and col. 1, first paragraph of FANARA), not with the administration of different active substances in a single dosage form and for this reason alone, one of ordinary skill in the art has no reason to consult FANARA for guidance in the latter respect.

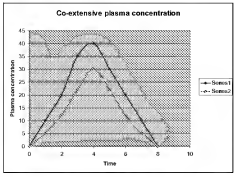
This is not persuasive because Fanara discloses "pharmaceutical compositions which can be administered orally, allowing the controlled release of pharmaceutically active substances such that a therapeutic effect is observed over fairly long periods, for example in only one or even two daily doses" (Col. 3, lines 22-27). Since the same or a second active substance are disclosed in the pharmaceutical compositions (Col. 2, lines 36-50), it is obvious that the therapeutic effect from the controlled release of the actives would be the result of the administration of the pharmaceutical composition.

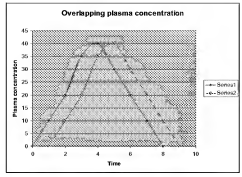
> Appellants argue that the passage in Fanara (Col. 2, lines 36-50) makes reference to active substances which have "very different pharmacokinetic profiles" and can be administered by means of the immediate/controlled release formulations of FANARA. Appellants argue that FANARA does not explain what exactly is to be understood by the phrase "very different pharmacokinetic profiles". Appellants argue that in this regard, it is pointed out that the term "pharmacokinetic profile"

encompasses a wide range of properties of a drug. Appellants submitted a definition of the term "pharmacokinetic profile" according to http://www.nature.com/nrg/journal/v4/n10/glossary/nrg1180_glossary.html and are "unable to see why the fact that Fanara mentions that the immediate/controlled release combinations set forth therein make it possible to obtain combined therapeutic effects by means of two active substances which have very different absorption, distribution and elimination characteristics in the body allegedly renders it obvious to one of ordinary skill in the art to use an immediate/controlled release combination for providing plasma concentrations in a therapeutic range of these two active substances in a way such that the therapeutically effective period of one drug overlaps at least about 70 % of the therapeutically effective period of the other drug".

This is not persuasive because the interpretation of claim 1 regarding the limitation "the dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70% of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug" can be as follows:

A or B





As the hypothetical figures above indicate, a person of ordinary skill in the art can interpret the 70% coextensive therapeutic range of the at least second drug as being 70% within the therapeutic range of the first drug (as in scenario A). The interpretation according to Scenario B is that there is 70% overlap between the therapeutic ranges of the first drug and the at least second drug.

Appellants state that "it further is noted that the above-cited passage of FANARA must be considered and assessed in the context of the entire disclosure of FANARA". Appellants argue that in lines 15-27 of col. 3, the inventors of FANARA make it clear that their contribution to the art does not rest in the provision of dosage forms which provide immediate/controlled release of two different active substances but rather that their invention consists in the provision of a new matrix composition for the controlled release part of corresponding dosage forms (and, primarily, for dosage forms which consist of only a single, controlled release composition), which matrix composition has certain advantages.

Appellants argue that one of ordinary skill in the art will understand that FANARA neither teaches nor suggests combined immediate/controlled release dosage forms

which are different from the known dosage forms in any respect other than the composition of the matrix for the controlled release portion thereof. Appellants argue that FANARA does not at all convey the impression that immediate/controlled release dosage forms are advantageous or even only suitable for each and every combination of two active substances.

This is not persuasive because the information provided in the background section (regarding the simultaneous administration of different drugs from a single dosage form) of the reference is relevant to one of ordinary skill in the art. Moreover, in light of the claim interpretation of co-extensive and overlapping therapeutic ranges of more than one drug in a single dosage form (as discussed above), the simultaneous administration of different drugs is rendered obvious.

Appellant points out the embodiments illustrated by Fanara in Example 4 and Example 7 and states that the fact that Fanara mentions only a few very specific examples of combinations of active substances for which the immediate/controlled release dosage forms (multilayer tablets) mentioned therein may be "particularly well suited" rather than pointing out that these multilayer tablets are advantageous with respect to the administration of any combination of two active substances is a clear indication that the inventors of FANARA were not at all concerned about the overlap of the periods of therapeutic effectiveness of these active substances. Appellants argue that there is not even a single passage in Fanara wherein the duration of action of any active substance is addressed and that whenever combinations of

active substances are mentioned in Fanara these combinations are to be contained in immediate release/controlled release dosage forms.

This is not persuasive because the teaching of the reference is not limited to the exemplified embodiments. Fanara teaches that "controlled-release pharmaceutical compositions can be used in combination with an immediate-release pharmaceutical composition for the same or for another active substance, in a single unit intended to be administered orally" (Col. 3, lines 32-37). This renders obvious the simultaneous or coextensive therapeutic range of more than one active drug in a single dosage form, as instantly claimed.

Since Fanara teaches a composition "where an active substance is released immediately and another active substance is released gradually, this makes it possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles" (Col. 2, lines 46-50). It would be obvious to one of ordinary skill in the art that with the varying release profiles of the different actives, the "combined therapeutic effects" would only be accomplished if the plasma concentrations of the actives were within or "substantially coextensive" with the therapeutically effective range of the two actives.

Appellants further point out that the Examiner apparently was unable to cite any document which in combination with Fanara could be considered to render it obvious to one of ordinary skill in the art to use the immediate/controlled release dosage forms set forth in Fanara for providing a plasma concentration within a therapeutic range of one drug over a period which is coextensive with at least about 70 % of the

period over which the plasma concentration of any other drug (and specifically, a morphine derivative having antitussive activity) is in the therapeutic range.

This is not persuasive because Fanara teaches antihistamines, antitussives, such as codeine, morphine, and their pharmaceutically acceptable salts, along with pseudoephedrine, and phenylepherine (Col. 4, lines 54-67). The limitation of the coextensive therapeutic ranges is discussed above.

10-b. Appellants argue that Fanara fails to render obvious independent claim 78.

Appellants argue that Fanara neither teaches nor suggests that the hydrocodone in one of the layers of the double-layer tablet of Example 7 can or should be replaced by a different morphine derivative and for this reason alone, fails to render obvious the subject matter of present independent claim 78 (and any of the claims dependent therefrom) as well.

This is not persuasive because Fanara teaches that "the same or a second active substance released gradually and regularly after administration ... makes it possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles" (Col. 2, lines 36-50). This teaching of Fanara renders obvious the limitation of two different morphine derivatives. One of ordinary skill in the art would find it obvious to combine two actives and would include two different morphine derivatives for a combined therapeutic effect.

(10) Response to Argument

10-a. Appellants argue that Fanara in view of Jaeger fails to render obvious independent claim 23.

Appellants argue that Jaeger is unable to cure the deficiency of a dosage form which releases two different drugs in a way such that the therapeutically effective period of one drug overlaps the therapeutically effective period of the other drug by at least about 70%.

This is not persuasive because in light of the claim interpretation of co-extensive and overlapping therapeutic ranges of more than one drug in a single dosage form (as discussed above), the simultaneous administration of different drugs with a coextensive therapeutic range would have been obvious over the teaching of Fanara that "where an active substance is released immediately and another active substance is released gradually, this makes it possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles" (Col. 2, lines 46-50)

Appellants are unable to see how the passage of JAEGER (Col. 3, lines 3-12) can render it obvious to combine codeine (phosphate) and an antihistamine, decongestant or expectorant in a dosage form (in particular, a bi-layered tablet) which provides the codeine and the second drug in way such that the period of plasma concentration within a therapeutic range of the antihistamine, decongestant or expectorant is coextensive with at least about 70 % of the period over which the plasma concentration of codeine is within a therapeutic range, and neither does the Final Office Action offer any explanation in this regard.

This is not persuasive because the limitation of the coextensive therapeutic range of two different active drugs in a single dosage form is addressed in the rejection over Fanara. Jaeger is used to cure the deficiency of codeine phosphate as the active substance. Since the primary reference, Fanara, teaches that more than one active substance can be used in a single dosage form with coextensive or overlapping therapeutic ranges, and Jaeger provides the teaching of an antitussive codeine composition, one of ordinary skill in the art would find it obvious to combine the two references. The motivation to combine Fanara with Jaeger is provided by the fact that both references are useful for the same purpose (i.e. antitussive). It would have been obvious to combine equivalents that are known for the same purpose. *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

10-b. Appellants argue that Fanara in view of Jaeger fails to render obvious independent claim 39.

Appellants argue that neither Fanara nor Jaeger teaches or suggests any multi-layered tablet which comprises a layer that contains a morphine derivate and a separate layer which comprises a decongestant, an expectorant, a mucus thinning drug, an analgesic and/or an antihistamine. Appellant argues that Fanara is primarily concerned with dosage forms which comprise only a single drug in a single matrix composition.

This is not persuasive because Fanara teaches that it is possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles (Col. 2, lines 36-50). One of ordinary skill in the art would

know from the teaching of Fanara that a single dosage form with multiple drugs having simultaneous or coextensive therapeutic ranges can be obtained.

Appellants argue that Example 2 of JAEGER describes a three-layered tablet, all three layers of which contain codeine phosphate and heptaminol (in different amounts), but no other drug. Appellants argue that JAEGER also mentions merely in passing (see the passage in col. 3 cited above in the context of claim 23) that the cold preparations described therein (Examples 1 and 3 describe coated single-layer tablets and a syrup, respectively) may optionally contain an additional drug selected from antihistamines, decongestants and expectorants. Appellants argue that these facts alone do not provide an apparent reason for one of ordinary skill in the art to incorporate an antihistamine, decongestant and/or expectorant into the three-layered tablet of Example 2.

This is not persuasive because Jaeger is combined with Fanara. Fanara teaches that more than one active substance can be used in a single dosage form with coextensive or overlapping therapeutic ranges. One of ordinary skill in the art would find it obvious to combine the single dosage form with multiple drugs having simultaneous or coextensive therapeutic ranges, as taught by Fanara, with the multi-layered tablet formulation comprising codeine phosphate and heptaminol, as taught by Jaeger, with a reasonable expectation of success in producing a functional multi-layered tablet with different active drugs in different layers with coextensive or overlapping therapeutic ranges.

10-c. Appellants argue that Fanara in view of Jaeger fails to render obvious independent claim 72.

Appellants argue that neither Fanara nor Jaeger address "any plasma half-lives, let alone any difference in the plasma half-lives of two drugs which are combined in a single dosage form".

This is not persuasive because Fanara teaches that it is possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles (Col. 2, lines 36-50). One of ordinary skill in the art would find it obvious that by choosing two different active substances, the plasma half-life of each drug can be determined during the process of routine experimentation. The limitation of the difference in plasma half-lives of two drugs would have been obvious given the drugs with different pharmacokinetic profiles and the determination of the plasma half lives.

10-d. Appellants argue that Fanara in view of Jaeger fails to render obvious independent claim 99.

Appellants argue that regarding the limitation of "at least one morphine derivative having antitussive activity" recited in claim 23 that is replaced by "codeine and pharmaceutically acceptable salts thereof" the Examiner has failed to establish a *prima facie* case of obviousness with respect to Fanara and Jaeger.

This is not persuasive because Fanara teaches antitussives such as codeine (Col. 4, lines 54-67). The obviousness of combining Fanara with Jaeger is discussed above (Page 15, point a).

10-e. Appellants argue that Fanara in view of Jaeger fails to render obvious dependent claims 12-14.

Appellants argue that Jaeger is completely silent as to the plasma half-life of any drug mentioned therein (and so is Fanara), let alone mentions any difference between the plasma half-lives of two drugs and that the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter of present claims 12-14 over Fanara in view of Jaeger.

This is not persuasive because regarding instant claims 12-14 one with ordinary skill in the art would use the teachings of Fanara and Jaeger to make a pharmaceutical composition by using drug combinations (antitussives, antihistamines, decongestants, expectorants) with drugs having different plasma half-lives in order to optimize the release of drugs over time. Drugs that are part of the immediate release would have a different plasma half-life than drugs that are part of the controlled release in order to maintain drug release for optimal therapeutic effect. The different plasma half-lives are intrinsic properties of the drug and cannot be separated from the drug. Since the references teach the drugs and the combinations of drugs, the different plasma half-lives are obvious. A chemical composition and its properties are inseparable (MPEP 2112.01).

10-f. Appellants argue that Fanara in view of Jaeger fails to render obvious dependent claim 26.

Appellants argue that they fail to see that Fanara and/or Jaeger teaches or suggests corresponding drug combinations, let alone in connection with a disclosure that the therapeutically effective periods of the drugs are to overlap the therapeutically effective periods of drugs by at least about 70%.

This is not persuasive because the limitation of the therapeutically effective periods of the drugs are to overlap the therapeutically effective periods of drugs by at least about 70% is obvious over the teaching of Fanara that a composition "where an active substance is released immediately and another active substance is released gradually, this makes it possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles" (Col. 2, lines 46-50). It would be obvious to one of ordinary skill in the art that with the varying release profiles of the different actives, the "combined therapeutic effects" would only be accomplished if the therapeutic ranges of the drugs were coextensive or overlapping.

10-g. Appellants argue that Fanara in view of Jaeger fails to render obvious dependent claim 33.

Appellants argue that claim 33 essentially recites that both layers of the bi-layered tablet of claim 23 are controlled release layers. Appellants note that the disclosure of

Fanara which relates to multi-layered tablets appears to be limited to combinations which comprise both an immediate release layer and a controlled release layer.

This is not persuasive because one of ordinary skill in the art would find it obvious to modify the different layers of the dosage form with various combinations of immediate release and/or controlled release layers during the process of routine experimentation based on the desired release profile.

Appellants argue that Jaeger does not address multi-layered tablets in general terms but discloses a three-layered tablet which appears to comprise an outer immediate release layer and two inner controlled release layers. Appellants argue that in addition to differing from the tablet of Example 2 of Jaeger in that it is only a bi-layered tablet which does not comprise an immediate release layer, the bi-layered tablet of instant claim 33 comprises at least one second drug (in a controlled release layer) selected from decongestants, expectorants, mucus thinning drugs, and antihistamines whereas the tablet of Example 2 of Jaeger comprises only a single drug, i.e., codeine phosphate.

This is not persuasive because one of ordinary skill in the art would recognize that the teaching of multi-layered tablets encompasses bi-layered tablets. The combination of only controlled release layers is an obvious variant of the multi-layered tablets disclosed by Jaeger. The limitation of at least one second drug would have been obvious because Jaeger is combined with Fanara. Since Fanara teaches that a second active substance can be incorporated, the combined teachings of Fanara and Jaeger render the limitations of dependent claim 33 obvious.

10-h. Appellants argue that Fanara in view of Jaeger fails to render obvious dependent claim 47.

Appellants argue that both Fanara and Jaeger are completely silent as to the plasma half-life of any drug mentioned therein, let alone mention any difference between the plasma half-lives of two drugs. Appellants argue that for this reason alone, the Examiner has failed to establish a prima facie case of obviousness of the subject matter of claim 47 over Fanara in view of Jaeger, even if one were to assume, arguendo, that the subject matter of independent claim 39 is rendered obvious by these two documents.

This is not persuasive because one with ordinary skill in the art would use the teachings of Fanara and Jaeger to make a pharmaceutical composition by using drug combinations (antitussives, antihistamines, decongestants, expectorants) with drugs having different plasma half-lives in order to optimize the release of drugs over time. Drugs that are part of the immediate release would have a different plasma half-life than drugs that are part of the controlled release in order to maintain drug release for optimal therapeutic effect. The different plasma half-lives are intrinsic properties of the drug and cannot be separated from the drug. Since the references teach the drugs and the combinations of drugs, the different plasma half-lives are obvious. A chemical composition and its properties are inseparable (MPEP 2112.01).

10-i. Appellants argue that Fanara in view of Jaeger fails to render obvious dependent claims 48 and 49.

Appellants argue that both Fanara and Jaeger are completely silent as to the plasma half-life of any drug mentioned therein, let alone mention any difference between the plasma half-lives of two drugs.

This is not persuasive because one with ordinary skill in the art would use the teachings of Fanara and Jaeger to make a pharmaceutical composition by using drug combinations (antitussives, antihistamines, decongestants, expectorants) with drugs having different plasma half-lives in order to optimize the release of drugs over time. Drugs that are part of the immediate release would have a different plasma half-life than drugs that are part of the controlled release in order to maintain drug release for optimal therapeutic effect. The different plasma half-lives are intrinsic properties of the drug and cannot be separated from the drug. Since the references teach the drugs and the combinations of drugs, the different plasma half-lives are obvious. A chemical composition and its properties are inseparable (MPEP 2112.01).

Appellants argue that additionally, as set forth in detail in sections VII.B.2.a. and VII.C.2.a. above with respect to independent claims 1 and 23, neither Fanara nor Jaeger address any overlap in the therapeutically active periods of two drugs which are provided by the same dosage form.

This is not persuasive because the limitation of the therapeutically effective periods of the drugs are to overlap the therapeutically effective periods of drugs by at least about 70% is obvious over the teaching of Fanara that a composition "where an active substance is released immediately and another active substance is released

gradually, this makes it possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles" (Col. 2, lines 46-50). It would be obvious to one of ordinary skill in the art that with the varying release profiles of the different actives, the "combined therapeutic effects" would only be accomplished if the therapeutic ranges of the drugs were coextensive or overlapping.

Appellants argue that the Final Office Action mailed October 19, 2007 does not even specifically mention claim 48, let alone explain why this claim allegedly is rendered obvious by Fanara in view of Jaeger.

The Final Office Action mailed October 19, 2007 discusses claim 47. As pointed out by the Appellant, claim 48 is dependent from claim 47 and claim 49 is dependent on claim 48. The limitations of claim 47 were discussed in the Final Office Action mailed October 19, 2007 on Page 11.

10-j. Appellants argue that Fanara in view of Jaeger fails to render obvious dependent claim 102.

Appellants argue that they fail to see that Fanara and/or Jaeger teaches or suggests corresponding drug combinations, let alone in connection with a disclosure that the therapeutically effective periods of the drugs (b) are to overlap the therapeutically effective periods of drug (a) by at least about 70%.

This is not persuasive because the limitation of the therapeutically effective periods of the drugs are to overlap the therapeutically effective periods of drugs by at least

about 70% is obvious over the teaching of Fanara that a composition "where an active substance is released immediately and another active substance is released gradually, this makes it possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles" (Col. 2, lines 46-50). It would be obvious to one of ordinary skill in the art that with the varying release profiles of the different actives, the "combined therapeutic effects" would only be accomplished if the therapeutic ranges of the drugs were coextensive or overlapping.

10-k. Appellants argue that Fanara in view of Jaeger fails to render obvious dependent claim 109.

Appellants argue that Claim 109 is dependent from independent claim 99 and essentially recites that both layers of the bi-layered tablet of claim 99 are controlled release layers. Appellants note that the disclosure of Fanara which relates to multi-layered tablets appears to be limited to combinations which comprise both an immediate release layer and a controlled release layer.

This is not persuasive because one of ordinary skill in the art would find it obvious to modify the different layers of the dosage form with various combinations of immediate release and/or controlled release layers during the process of routine experimentation based on the desired release profile.

Appellants argue that Jaeger does not address multi-layered tablets in general terms but discloses a three-layered tablet which appears to comprise an outer immediate

release layer and two inner controlled release layers. In addition to differing from the tablet of Example 2 of JAEGER in that it is only a N-layered tablet which does not comprise an immediate release layer, the bi-layered tablet of instant claim 109 comprises at least one second drug (in a controlled release layer) selected from decongestants, expectorants, mucus thinning drugs, and antihistamines whereas the tablet of Example 2 of JAEGER comprises only a single drug, i.e., codeine phosphate.

This is not persuasive because one of ordinary skill in the art would recognize that the teaching of multi-layered tablets encompasses bi-layered tablets. The combination of only controlled release layers is an obvious variant of the multi-layered tablets disclosed by Jaeger. The limitation of at least one second drug would have been obvious because Jaeger is combined with Fanara. Since Fanara teaches that a second active substance can be incorporated, the combined teachings of Fanara and Jaeger render the limitations of dependent claim 109 obvious.

Response to Argument

D. Appellants argue that claims 8-11, 37, 45, 46, 112 and 113 are not properly rejected under 35 U.S.C. 103(a) as unpatentable over Fanara in view of Jaeger in further view of Findlay

Appellants note that claims 8-11, 37, 45, 46, 112 and 113 depend, directly or indirectly, from independent claims 1 (claims 8-11), 23 (claim 37), 39 (claims 45 and 46) and claim 99 (claims 112 and 113). Appellants state that as set forth in detail in

sections VII.B.2.a., VII.C.2.a., VII.C.2.b. and VII.C.2.d., (of the Appeal Brief filed 10/20/08) neither of claims 1, 23, 39 and 99 is rendered obvious by Fanara or Fanara in view of Jaeger. It is submitted that for this reason alone, the Examiner has failed to establish a prima facie case of obviousness of dependent claims 8-11, 37, 45, 46, 112 and 113 over Fanara in view of Jaeger in further view of Findlay.

This is not persuasive because obviousness based on Fanara, and the combination of Fanara and Jaeger is discussed in detail above. Findlay is used to cure the deficiency of chlorpheniramine, promethazine and guaifenesin. It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the pharmaceutical composition with combined therapeutic effects of more than one active substance, as suggested by Fanara, in view of the codeine phosphate and second active substances (antihistamines, decongestants, and expectorants) as suggested by Jaeger and further in view of the specific antihistamines and expectorant as suggested by Findlay and produce the instant invention. One of ordinary skill in the art would have been motivated to do this because the specific active substances taught by Findlay supplement the antitussive first drugs for ameliorating cough symptoms. All the references are useful for the same purpose (i.e. antitussive). It would have been obvious to combine equivalents that are known for the same purpose. *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

(10) Response to Argument

For the above reasons, it is believed that the rejections should be sustained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

This examiner's answer contains a new ground of rejection set forth in section **(9)** above. Accordingly, appellant must within **TWO MONTHS** from the date of this answer exercise one of the following two options to avoid *sua sponte* **dismissal of the appeal** as to the claims subject to the new ground of rejection:

(1) **Reopen prosecution.** Request that prosecution be reopened before the primary examiner by filing a reply under 37 CFR 1.111 with or without amendment, affidavit or other evidence. Any amendment, affidavit or other evidence must be relevant to the new grounds of rejection. A request that complies with 37 CFR 41.39(b)(1) will be entered and considered. Any request that prosecution be reopened will be treated as a request to withdraw the appeal.

(2) **Maintain appeal.** Request that the appeal be maintained by filing a reply brief as set forth in 37 CFR 41.41. Such a reply brief must address each new ground of rejection as set forth in 37 CFR 41.37(c)(1)(vii) and should be in compliance with the other requirements of 37 CFR 41.37(c). If a reply brief filed pursuant to 37 CFR 41.39(b)(2) is accompanied by any amendment, affidavit or other evidence, it shall be treated as a request that prosecution be reopened before the primary examiner under 37 CFR 41.39(b)(1).

Extensions of time under 37 CFR 1.136(a) are not applicable to the TWO MONTH time period set forth above. See 37 CFR 1.136(b) for extensions of time to reply for patent applications and 37 CFR 1.550(c) for extensions of time to reply for ex parte reexamination proceedings.

Respectfully submitted,

/Aradhana Sasan/
Examiner, Art Unit 1615

A Technology Center Director or designee must personally approve the new ground(s) of rejection set forth in section (9) above by signing below:

/Michael G. Wityshyn/
Acting Director, Technology Center 1600

Conferees:

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615

/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612